Advancing Drug Development for the Prevention and Treatment of Respiratory Syncytial Virus Infections
Initiation of Pediatric Trials: RSV Bronchiolitis

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Medical Officer, Division of Antiviral Products
Center for Drug Evaluation and Research, FDA
Objectives

• Discuss the types of studies that support initiation of pediatric trials for treatment and prevention products:
  – Which adult populations/disease conditions are preferred?
  – Are adult challenge studies adequate to demonstrate prospect of benefit for infants in bronchiolitis trials?
  – To what extent can non-clinical data be used to support pediatric studies (i.e., animal models of disease)?
Regulatory Framework for Pediatric Clinical Trials

• 21 CFR 50 Subpart D: Additional Safeguards for Children in Clinical Investigations

• Clinical trials in which more than minimal risk to children is presented by an intervention or procedure…may involve children only if...
  (a) The risk is justified by the anticipated benefit to the subjects;
  (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
  (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.
Standard Approach to Pediatric Antiviral Drug Development

• Initial clinical trials to establish safety and efficacy are conducted in adults

• If the infection results in a comparable disease course in adults and children, efficacy in adults can be extrapolated to children
  – Primary objectives of pediatric studies are to evaluate PK and safety
RSV Bronchiolitis

- Conventional paradigm doesn’t apply to RSV drug development
- Natural history of bronchiolitis differs from lower respiratory tract infection in older children and adults
  - Anatomy and physiology
  - Host immune response
- Efficacy cannot be extrapolated
Initiation of Pediatric RSV Trials

Data from adult clinical trials and nonclinical studies should:

• Demonstrate prospect for clinical benefit
• Characterize the drug’s adverse event profile
TREATMENT OF BRONCHIOLITIS
Treatment of Bronchiolitis

- It is unknown whether reduction of viral load in adults predicts efficacy in treatment of bronchiolitis.
- However, evidence of symptomatic improvement in adults supports the prospect of clinical benefit in infants and young children.
- Therefore, we recommend evaluating both antiviral activity AND clinical signs/symptoms in early phase adults trials.
Populations for Supportive Efficacy Studies

• Patients at risk for severe illness from naturally acquired RSV infection:
  – Elderly adults
  – Immunocompromised adults

• Healthy adults experimentally infected with an acceptable RSV challenge strain
Trial Design for Supportive Efficacy Studies

- Randomized, double-blind, comparative trials are preferred
- Other Possibilities
  - Dose-ranging
  - Duration of treatment
- Subjects should have established infection prior to receiving the investigational product
Endpoints for Supportive Efficacy Studies

• Multiple virologic and clinical endpoints could be explored in Phase 2 studies

• Examples:
  – Change in RSV viral load
  – Change in clinical symptom scores
  – Hospitalization
    • Duration of hospitalization
    • Mechanical ventilation
  – Other indicators of disease progression/resolution
PREVENTION OF BRONCHIOLITIS
Prevention of Bronchiolitis

• Historically, focus has been on passive immunoprophylaxis
  – Scientific basis from observational studies of RSV infection in young infants, which revealed a correlation between circulating maternal anti-RSV antibody levels and decreased severity of disease

• Development of new products for RSV prophylaxis may need supportive evidence of prophylactic activity prior to pediatric trials
Populations for Supportive Efficacy Studies

• Similar to treatment trials
• Patients at risk for symptomatic illness from naturally acquired RSV infection:
  – Elderly adults
  – Immunocompromised adults
• Healthy adults – challenge studies
Trial Design for Supportive Efficacy Studies

• Randomized, double-blind, comparative trials are preferred
  – Naturally acquired infection: conduct studies in areas with documented RSV disease activity
  – Challenge studies: subjects receive the investigational product prior to experimental inoculation
• Data from trials conducted for RSV treatment may also support prophylaxis trials (e.g. oseltamavir for influenza)
Endpoints for Supportive Efficacy Studies

• Multiple clinical endpoints could be explored in Phase 2 studies

• Examples:
  – Prevention of symptomatic illness (laboratory confirmed)
  – Prevention of LRTI
  – Prevention of hospitalization

• Sponsors should discuss proposed endpoints with the Agency during protocol development
Safety Considerations: Treatment and Prophylaxis

• At least 100 adults should be exposed to the drug prior to initiating pediatric trials
  – Exposures should be similar or higher than the proposed pediatric dosage regimen

• Additional data in adults may be needed prior to initiation of pediatric trials depending on:
  – Nonclinical pharmacology/toxicology findings
  – Preliminary safety profile of the drug observed in adults
NON-CLINICAL STUDIES
Role of Nonclinical Studies in Pediatric RSV Drug Development

• Data from nonclinical studies may be used to support both the safety and efficacy of investigational products
• Studies in juvenile and adult animals may serve to fill in the gaps from adult clinical studies
Nonclinical Studies: Safety

• Studies in juvenile animals are recommended, in addition to the standard nonclinical assessments.

• Results from juvenile toxicology studies may inform risk for toxicity in young children that otherwise may not be detected.
Nonclinical Studies: Efficacy

• Data from adult clinical trials have limited applicability to trials of infants with bronchiolitis
• Animal models may resemble bronchiolitis more closely
• Therefore, data from applicable nonclinical studies may provide important evidence of supportive efficacy to support initiation of pediatric trials for treatment and prophylaxis agents
Summary

• There is a regulatory requirement for the prospect of clinical benefit in pediatric trials

• Supportive efficacy data can be obtained from studies in adults with naturally acquired RSV infection or healthy adults who are experimentally inoculated with RSV challenge strains

• Differences in the natural history of RSV disease in infants versus older children/adults limits the applicability of data between populations

• Safety and efficacy data from adult studies can be augmented with nonclinical studies in juvenile and adult animals
THANK YOU
Burden, Outcomes and Image of RSV in Elderly & High-risk Persons

Edward Walsh
University of Rochester
Rochester General Hospital

1471 hospitalizations at one hospital during 4 winters using PCR, serology & culture:

RSV 10.6% vs. Flu 11.6%

Conversion to population base >65 yo
77 hospitalizations/100,000 (86 for Zhou)

Falsey AR, et al. NEJM 205; 352:1749-59
Percent Admissions: RSV and Flu A in 1471 admissions to RGH

Average

RSV - 9.0 %
Flu A - 9.5 %

Falsey et al NEJM 2005;352:1749
508 hospitalized adults ≥ 65 years
PCR over 3 winters in Nashville, TN

<table>
<thead>
<tr>
<th>Virus</th>
<th>Incidence (%)</th>
<th>% ICU</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>6.1%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6.5%</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>HMPV</td>
<td>4.5%</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Recent data from Hong Kong
Lee N, et al. CID 2013; 57:1572

Retrospective 3 years at 3 hospitals
Diagnosed RSV & Flu by FA on nasal aspirates

Results: 607 RSV  547 Flu

Negative binomial regression model of Flu and RSV by utilizing respiratory and circulatory hospitalization data from 13 states (HCUP) and national lab diagnostic data

≥ 65 yrs: 86/100,000 person-yrs (309 flu)
50-64 yrs: 12.8/100,000 person-yrs (65 flu)
<1 yr: 2,345/100,000 person-yrs
1-4 yrs: 178/100,000 person-yrs

Conversion to number of RSV associated US hospitalizations by age group

43,420 adults >50 years of age
122,280 infants & children <5 yrs
Poisson regression model to estimate mortality from RSV & Flu in elderly adults in The Netherlands.

During 9 years Influenza ~1.6 fold > RSV

<table>
<thead>
<tr>
<th>Virus</th>
<th>65-74 yr</th>
<th>75-84 yr</th>
<th>≥ 85</th>
<th>≥ 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu A</td>
<td>1,935</td>
<td>6,282</td>
<td>7,201</td>
<td>15,519</td>
</tr>
<tr>
<td>RSV</td>
<td>1,305</td>
<td>5,171</td>
<td>7,425</td>
<td>13,902</td>
</tr>
<tr>
<td>Flu B</td>
<td>2,209</td>
<td>3,907</td>
<td>6,116</td>
<td></td>
</tr>
</tbody>
</table>
### Estimated hospitalization burden associated with influenza & RSV in NYC 2003-2011

*Goldstein E. Influenza and other Respiratory Viruses 2015;9:225-233*

<table>
<thead>
<tr>
<th>Rate per 100,000 persons</th>
<th>50-64 yrs</th>
<th>65-74 yrs</th>
<th>≥75 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flu</td>
<td>RSV</td>
<td>Flu</td>
</tr>
<tr>
<td>Respiratory Assoc. Hospitalizations</td>
<td>66</td>
<td>27</td>
<td>126</td>
</tr>
<tr>
<td>P &amp; I</td>
<td>26</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>Chronic Lung Resp Dis</td>
<td>29</td>
<td>7</td>
<td>55</td>
</tr>
<tr>
<td>Circulatory Diseases</td>
<td>-20</td>
<td>37</td>
<td>-40</td>
</tr>
</tbody>
</table>
Office RSV and Influenza 1995-8
Zambon MC. Lancet 358:1410-16, 2001

<table>
<thead>
<tr>
<th>Age Group</th>
<th>% of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>430</td>
</tr>
<tr>
<td>5..14</td>
<td>314</td>
</tr>
<tr>
<td>15..44</td>
<td>949</td>
</tr>
<tr>
<td>45..64</td>
<td>321</td>
</tr>
<tr>
<td>&gt;65</td>
<td>167</td>
</tr>
</tbody>
</table>
Recent Marshfield Clinic data

1568 adults > 50 yo presenting with MAARI over 6 season

Sundaram ME.
CID 2013; 57:789

<table>
<thead>
<tr>
<th>Virus</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>343</td>
<td>21.9</td>
</tr>
<tr>
<td>RSV</td>
<td>170</td>
<td>10.8</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>126</td>
<td>8.0</td>
</tr>
<tr>
<td>hMPV</td>
<td>125</td>
<td>8.0</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>122</td>
<td>7.8</td>
</tr>
</tbody>
</table>

1326 MAARI cases with 154 RSV (12%) in 4 year period

McClure DL.
PLOS ONE 9:e1025886

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Incidence/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>124 (99,156)</td>
</tr>
<tr>
<td>60-69</td>
<td>147 (110,196)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>199 (153,258)</td>
</tr>
</tbody>
</table>
Modelling of burden of RSV in adults & elderly in UK*

*Fleming DM. BMC Infectious Diseases 2015; 15:443*

<table>
<thead>
<tr>
<th></th>
<th>GP visits</th>
<th>Hospitalizations</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>18+ yrs:</td>
<td>487,247</td>
<td>17,799</td>
<td>8,484</td>
</tr>
<tr>
<td>65+ yrs:</td>
<td>175,070</td>
<td>14,039</td>
<td>7,915</td>
</tr>
</tbody>
</table>

High-risk** were 2x more likely to visit a GP and 4x more likely to be hospitalized with a respiratory illness than low-risk persons

* Population of UK 60 million
**defined as COPD, CHF, DM, liver disease, Cerebrovascular disease, MS
Outcomes in Healthy Elderly

- RSV
- Influenza A

Call MD
Office
ED
Admitted

Percent
Outcomes in High-Risk Cohort

- RSV
- Influenza A

Percentages for different outcomes:
- Call MD
- Office
- ED
- Admitted
Viral load according to severity

Mean RSV titer by day after symptom onset

<table>
<thead>
<tr>
<th></th>
<th>RSV</th>
<th>Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Time to admission</td>
<td>2.6 d</td>
<td>2.0 d</td>
</tr>
<tr>
<td>T &gt;37.5 C</td>
<td>75%</td>
<td>94%</td>
</tr>
<tr>
<td>wheezing</td>
<td>69%</td>
<td>53%</td>
</tr>
<tr>
<td>COPD present</td>
<td>36%</td>
<td>24%</td>
</tr>
<tr>
<td>Ventilation</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>Death</td>
<td>9%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Nasal vs. sputum titers

<table>
<thead>
<tr>
<th>Peak titer (log_{10} pfu/ml)</th>
<th>Mild disease (n = 61)</th>
<th>Severe disease (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>2.3 ± 1.2</td>
<td>2.8 ± 1.3</td>
<td>.09</td>
</tr>
<tr>
<td>Sputum</td>
<td>2.5 ± 1.8</td>
<td>3.3 ± 1.8</td>
<td>.06</td>
</tr>
</tbody>
</table>

100-1000 x lower than in infants
## Shedding duration in adults with natural RSV infection

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>Mild disease (n = 61)</th>
<th>Severe disease (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>10 ± 5</td>
<td>13 ± 6</td>
<td>.003</td>
</tr>
<tr>
<td>Sputum</td>
<td>9 ± 4</td>
<td>10 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Encounter</td>
<td>Status</td>
<td>Date</td>
<td>Time</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>------------</td>
<td>-------</td>
</tr>
<tr>
<td>Orders Only</td>
<td>Admission</td>
<td>04/05/16</td>
<td>09:06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appointment</td>
<td>04/03/16</td>
<td>10:51</td>
</tr>
<tr>
<td></td>
<td>Appointment</td>
<td>03/02/16</td>
<td>11:15</td>
</tr>
<tr>
<td></td>
<td>Appointment</td>
<td>02/02/16</td>
<td>11:55</td>
</tr>
<tr>
<td></td>
<td>Appointment</td>
<td>12/24/15</td>
<td>10:30</td>
</tr>
</tbody>
</table>

**Progress Notes**

No notes of this type exist for this encounter.

**Diagnoses**

- COPD exacerbation - Primary
  - ICD-10-CM: J44.1
  - ICD-9-CM: 491.21

**Medications Ordered This Encounter**

- **albuterol 90 mcg/actuation Ihl inhaler**
  - Inhalation: 2 puffs into the lungs every 6 (six) hours as needed for Wheezing or Shortness of Breath - Inhalation
  - Disp: 1 Inhaler
  - Refills: 0
  - Start: 4/5/2016
  - End: 4/5/2016

**Orders**

**Created by**

Katherine Kristine Copie, FNP on 04/05/2016 09:06 AM

Reprint Req (In-process or resulted tests will not reprint)

Reprint Requisition
RAPID RSV BY PCR

DETECTED  Sensitivity: >90%  Specificity: >90%

The performance characteristics of the Simplexa RSV assay are dependent on the circulating strain of respiratory syncytial virus. The Simplexa RSV assay compares closely to culture.
Reason for Admission

- Hypotension, unspecified hypotension type - Primary
- Hyperkalemia
- Dehydration
- Diabetes mellitus
- CKD (chronic kidney disease) stage 4, GFR 15-39 ml/min